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# Molecular Mechanics (MM3) Parameterization for Oxocarbenium Ions

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*Received 16 June 1999; accepted 21 September 1999*

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**ABSTRACT:** The physical properties of a diverse group of 12 oxocarbenium ions have been studied with *ab initio* calculations at the MP2/6-31+G\* level of theory. Based on theoretically derived properties such as molecular equilibrium geometry, dipole moment, and vibrational frequencies, a molecular mechanics (MM3) force field has been developed with the assistance of the programs TORSIMART and MPMSR, components of our artificial parameter development and refinement method. The MM3 force field is now able to reproduce bond lengths, bond angles, moments of inertia, dipole moments, torsional energy profiles, and vibrational frequencies of oxocarbenium ions, which will allow further studies of glycoside hydrolysis and their rates of reaction. © 2000 John Wiley & Sons, Inc. J Comput Chem 21: 329–339, 2000

**Keywords:** molecular mechanics; MM3; force field; parameterization; carbohydrate hydrolysis; oxocarbenium ion

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Contract/grant sponsor: Tripos, Inc.

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## Introduction

Carbohydrates are an important class of molecules in living systems, and their reactions are of significant interest. Oxocarbenium ions are the accepted reaction intermediates in the acid-catalyzed hydrolysis of glycosides, and it is believed that the rates of the hydrolysis are heavily dependent on the stability of those intermediate species.<sup>1</sup> Toullec reported that C—H acidity in acyclic oxocarbenium ions affect the hydrolysis rate of the parent acetals, and that nonsteric interactions play an important role.<sup>2</sup> At the same time, Amyes and Jencks observed a short-lived oxocarbenium ion intermediate.<sup>3</sup> In an effort to explore the steric effects and stability of oxocarbenium ions quantitatively, various computational methods may be considered. Semiempirical methods may not be sufficiently accurate to carry out this research. High level *ab initio* calculations would be desirable, but for large chemical systems, such as those of biological interest, *ab initio* calculations are generally intractable. Molecular mechanics (MM3)<sup>4</sup> is an attractive choice, as it combines efficiency with accuracy, but additional parameters were required to competently model oxocarbenium ions.

A set of MM2(87)<sup>5</sup> parameters for oxocarbenium ions was previously developed in our laboratories.<sup>6</sup> We now have the ability to reproduce bond lengths, bond angles, torsion angles, and moments of inertia with greater accuracy, using MM3(2000).<sup>7</sup> More complex potential functions and the addition of cross terms (e.g., bend–bend, stretch–bend and torsion–stretch interactions) allow better molecular mechanics results, but more parameters are required. To develop these, MM3 requires consideration of extensive criteria, including vibrational frequencies and their vibrational modes, during parameterization.

## Computational Method

Oxocarbenium ion parameterization occurred in two stages. In the first phase we optimized torsional parameters, and in the second we optimized all other parameters. Due to the marked lack of experimental data on oxocarbenium ions, all parameters developed in this work are based on *ab initio* results.

In the MM3 program, three parameters ( $V_1$ ,  $V_2$ , and  $V_3$ ) are used to describe the potential energy

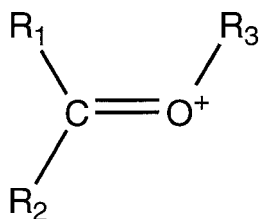
curve of a torsional rotation, also referred to as a torsional energy profile. Torsional energy may not be attributed to any one physical effect; it is mainly invoked in molecular mechanics to make up the deficiencies of many interactions. For example, the  $V_1$  term is used to supplement the deficiencies in dipole–dipole and van der Waals interactions. The  $V_2$  term is used to describe hyperconjugation effects, while the  $V_3$  term represents steric and orbital effects.<sup>8</sup> An energy term separate from the torsional energy is calculated in the MM3 program for 1,4-nonbonded interactions. For the development of the torsional parameters, a model energy profile is mapped out with a series of *ab initio* calculations, driving the angle of interest from 0 to 180 (or 360, if the rotation is not symmetrical) degrees. At each point, the dihedral angle is fixed to a specific value, while all other degrees of freedom are fully optimized. To achieve more accurate mapping of minima and maxima, an additional calculation is performed near each stationary point, without any constraints. In this study, 12 profiles were mapped by driving each torsion angle from 0 to 180 degree in 15-degree increments. TORS MART<sup>9,10</sup> was used to develop the MM3  $V_1$ ,  $V_2$ , and  $V_3$  parameters by fitting MM3 torsional profiles to those generated by *ab initio* methods.

Additional MM3 parameters such as stretching and bending force constants, equilibrium bond lengths and bond angles, bond moments, and electronegativity corrections were also developed. Because there is so much interdependence among the parameters, the molecular mechanics force field can be complicated. A single parameter may affect multiple geometric features; conversely, one feature's value may be affected by more than one parameter. The data necessary for these parameterizations include bond lengths, bond angles, torsion angles, moments of inertia, dipole moments, and vibrational frequencies. During parameterization, all of the data being fit must be monitored, ideally resulting in simultaneous optimization of multiple variables. Therefore, the most important task in molecular mechanics parameterization will be balancing all of the factors to produce the best overall fit.

MPMSR<sup>9,10</sup> was used to develop MM3 parameters based on structural data and vibrational spectra. By simulating the intuition-guided trial-and-error method, MPMSR optimizes one parameter while the others are held constant. During this optimization, MPMSR monitors the differences between the MM3 calculated results and those obtained from

experimental methods and/or *ab initio* calculations. All five criteria (bond lengths, bond angles, dipole moments, moments of inertia, and vibrational frequencies) contribute to the global fitting index. The importance of each criterion, however, may vary, depending on the system; therefore, the user's decision of how to weight the data directly affects the quality of a molecular mechanics force field. In this way, our MPMSR method is different from previous computerized least squares fitting methods.

Because few experimental data are available for oxocarbenium ion parameterization, *ab initio* calculations were carried out for a set of twelve training molecules (Fig. 1). The theoretically obtained structural data and vibrational spectra were used as templates in the development of MM3 parameters. It is important to note that MM3 bond lengths are reported as  $r_g$ , while the *ab initio* data is reported as  $r_e$ . No conversion between the two methods was employed. All structural data were taken directly from the MP2/6-31+G\* *ab initio* results, and vibrational frequencies were scaled by a factor of 0.95 (0.975 for OH stretching mode).<sup>11</sup> All *ab initio* calculations reported in this manuscript were done using Gaussian 92<sup>12</sup> on IBM R6000-580 workstations. All MM3 calculations were carried out utilizing MM3(94), and later MM3(2000),<sup>7</sup> on Silicon Graphics workstations. MPMSR and TORSIMART were run on SGI, IBM R6000, and Dec5100 workstations. The Sybyl 6.0<sup>13</sup> software package was also used for convenient graphical interfaces to both Gaussian and MM3.



	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>		R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>
1:	H	H	CH <sub>3</sub>	7:	H	H	CH <sub>2</sub> CH <sub>3</sub>
2:	H	CH <sub>3</sub>	CH <sub>3</sub>	8:	H	H	CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
3:	CH <sub>3</sub>	H	CH <sub>3</sub>	9:	H	H	CH <sub>2</sub> CH <sub>2</sub> OH
4:	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	10:	H	CH <sub>2</sub> OH	CH <sub>3</sub>
5:	H	CH <sub>2</sub> CH <sub>3</sub>	CH <sub>3</sub>	11:	H	CH <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> OH
6:	CH <sub>2</sub> CH <sub>3</sub>	H	CH <sub>3</sub>	12:	H	CH <sub>2</sub> CH <sub>2</sub> OH	CH <sub>3</sub>

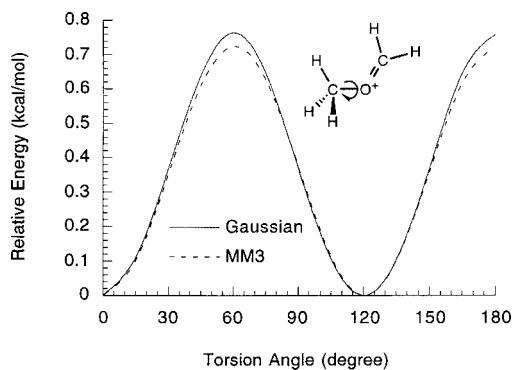
**FIGURE 1.** Twelve training molecules used in this MM3 parameterization.

## Results and Discussion

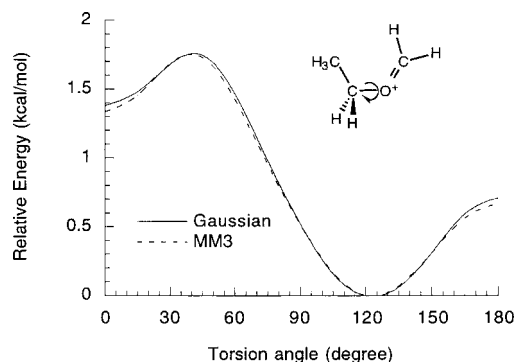
### TORSIONAL ENERGY PROFILES AND TORSIONAL PARAMETERS

*Ab initio* torsional profiles were calculated for most of the torsional constants in the parameter set of oxocarbenium ions at the MP2/6-31+G\* level of theory.<sup>14</sup> In general, three types of torsional profiles were encountered in this work. The first type, as shown in Figure 2, involves an interaction between a single bond (C—H, also C—C and O—O, not shown) and a double bond (O<sup>+</sup>=C). Because of the dipole-dipole interaction and/or dipole-induced dipole interaction caused by the presence of the double bond, these torsion angles favor the eclipsed conformation. Due to the three-fold symmetry of the methyl group rotation, a rotatable bond with a methyl group terminus (H—C—O<sup>+</sup>=C, also H—C—C—O<sup>+</sup> not shown) has three identical minima at 0, 120, and 240 degrees. This threefold symmetric structure eliminates the need for  $V_1$  and  $V_2$  terms, leaving only the  $V_3$  term in the torsional energy equation. The only profile of this type that does not have an eclipsed global minimum is the C—C—O<sup>+</sup>=C (1—1—70—71) torsion, as shown in Figure 3. The strong steric effects between the hydrogen atoms in the terminal methyl group and the hydrogen atoms on the sp<sup>2</sup> carbon atom increase the potential energy of the eclipsed conformation so dramatically that it is no longer the global minimum.

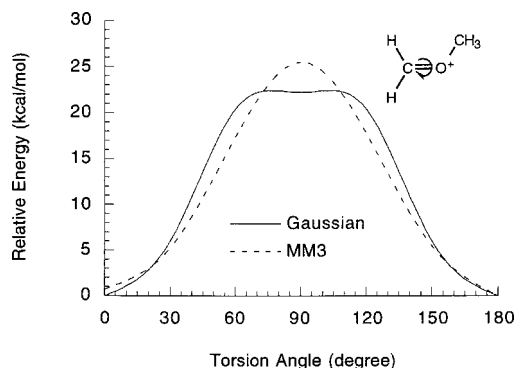
The second type of torsional profile, characterized by three minima (two *gauche* and one *trans*) is shown in Figure 4. The profiles of this type are mainly controlled by steric interactions. Similar to the first set of profiles, the rotatable bonds with a methyl group terminus (for example H—C—C—



**FIGURE 2.** Torsional energy profiles for the term H—C—O<sup>+</sup>=C (5—1—70—71).



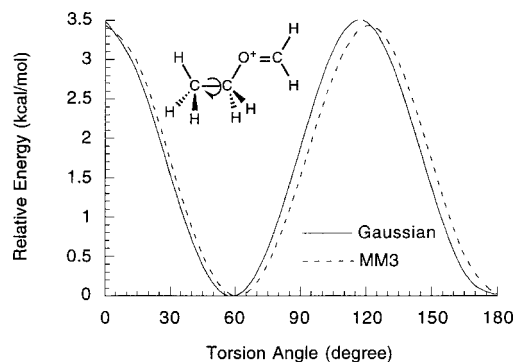
**FIGURE 3.** Torsional energy profiles for the term  $\text{C}-\text{C}-\text{O}^+=\text{C}$  (1—1—70—71).



**FIGURE 5.** Torsional energy profiles for the term  $\text{H}-\text{C}=\text{O}^+-\text{C}$  (5—71—70—1).

$\text{O}^+$ , as shown in Fig. 4) have three identical minima at angles of 60, 180, and 300 degrees. Again, only the  $V_3$  term is nonzero in this set of torsional parameters. The other three torsional profiles of this type do not have a symmetric rotation, and require all three torsional terms ( $V_1$ ,  $V_2$ , and  $V_3$ ) to describe the energy curve. These three asymmetric torsional profiles all have lower energy at the *gauche* conformations than the *trans* because dipole-dipole and/or dipole-induced dipole interactions also contribute to the torsional energy profiles. The dominant steric interactions dictate the preference of the *trans* and *gauche* conformations as opposed to the eclipsed (*cis*) and partial eclipsed (*synclinal*) conformations favored by the dipole-dipole interactions. Because the dipole-dipole interaction also plays a role in determining the shape of the torsional energy profiles, the potential energies for the *trans* conformations increase, leaving the *gauche* conformation as the global minimum.

The third type of torsional energy profile in our oxocarbenium ion force field involves the rotation about a double bond, as shown in Figure 5. This



**FIGURE 4.** Torsional energy profiles for the term  $\text{H}-\text{C}-\text{C}-\text{O}^+$  (5—1—1—70).

profile, as would be expected, has minima at 0 and 180 degrees, and high energy maxima at 90 and 270 degrees. Because of the symmetric rotation,  $\text{H}-\text{C}_{\text{sp}2}=\text{O}^+-\text{C}$  (5—71—70—1) has a two-fold symmetric torsional profile with two minima of identical energy. In contrast, the two minima in the  $\text{C}-\text{C}_{\text{sp}2}=\text{O}^+-\text{C}$  (1—71—70—1) torsion have different energies, with the *trans* conformation about 2.5 kcal/mol lower than the *cis* conformation. In considering the MM3 torsional potential function,  $V_1$  and  $V_3$  may be eliminated, and this torsional energy profile can be described by a pure  $V_2$  term.

TORSMART<sup>9,10</sup> was used to develop most of the torsional parameters involved above, augmented by the traditional and highly successful “inspection method” of parameter fitting. For each set of  $V_1$ ,  $V_2$ , and  $V_3$ , TORSMART will adjust one, two, or all three parameters as necessary, until MM3 closely reproduces the desired *ab initio* profile. Due to the interdependence of the different types of parameters, however, the optimum values of a set of torsional parameters may change after the values of other parameters are altered. For this reason, the procedure is iterated until all parameters reach optimum values.

A torsional energy profile, in most cases, is actually affected by more than one torsional term. For example, the torsional profile shown in Figure 3 is a combination of one  $\text{C}-\text{C}-\text{O}^+=\text{C}_{\text{sp}2}$  (atom type 1—1—70—71) torsion and two  $\text{H}-\text{C}-\text{O}^+=\text{C}_{\text{sp}2}$  (5—1—70—71) torsions with about 120 degrees phase difference between any two of them. To use this profile to determine the parameter set of  $\text{C}-\text{C}-\text{O}^+=\text{C}_{\text{sp}2}$ , the term of  $\text{H}-\text{C}-\text{O}^+=\text{C}_{\text{sp}2}$  must be determined previously (see Fig. 2). The initial molecular mechanics torsional parameterization should start from a profile that consists of only one set of unknown torsional terms, like the one shown in

Figure 2. Generally, a series of torsional parameterizations should be carried out in such a way that each torsional profile contains only one unknown torsional term. However, because there are indirect interactions among parameters, various torsional parameters will affect a profile even if one unknown torsion is isolated. Iteratively adjusting the parameters for all profiles until they are mutually optimized minimizes this effect and stabilizes the final parameters.

## OTHER PARAMETERS

MPMSR<sup>9,10</sup> was used to develop other parameters (e.g., equilibrium bond lengths, equilibrium bond angles, stretching constants, bending constants, out-of-plane bending constants, and bond dipoles). As discussed previously, the order of the parameterization and the weight given to each criterion are important factors in obtaining a satisfactory parameter set. In this oxocarbenium ion parameterization, torsional parameters were optimized first, followed by bond lengths, bond angles, bond moments, stretching force constants, bending force constants, and electronegativity parameters. To reduce the effect of sequencing, reparameterizations were carried out stepwise until the all of the desired features were adequately reproduced by MM3. This reparameterization also included the torsional parameters, because those values will affect non-torsional terms.

In this work a set of twelve training molecules was used to develop the MM3 parameters. All twelve molecules were fully optimized in Gaussian 92 at the MP2/6-31+G\* level of theory. Single-point calculations were then carried out at the same level of theory to obtain the vibrational frequencies. To assure that the MM3 and *ab initio* conformations were comparable, Sybyl was used to retrieve the Gaussian optimized geometries and generate MM3 input files from these optimized coordinates. Next, MPMSR carried out MM3 optimizations for each of the training molecules using a set of initial test parameters. The trial parameter file was then modified to reduce the deviations between the *ab initio* data and MM3 results. This process was repeated until no further improvement could be detected upon adjustment of any parameter. Because torsional parameters may be significantly coupled with other parameters, applying TORSMAST and MPMSR together allows an efficient determination of the best parameter set for all important criteria.

The final MM3 parameters for oxocarbenium ions are reported in Table I. Using these parameters,

**TABLE I.** MM3 Parameter Set for Oxocarbenium Ions.<sup>a</sup>

Bond stretching parameters				
Bond	$l_0$ (Å)	$k_S$		
C—O <sup>+</sup>	1.4890	7.40		
C=O <sup>+</sup>	1.2500	8.50		
C—C(=O <sup>+</sup> )	1.5030	4.80		
H—C(=O <sup>+</sup> )	1.0920	5.10		
Angle bending parameters				
Atoms	$k_q$	$q_0$ (degrees)		
		Type 1	Type 2	Type 3
C—C(=O <sup>+</sup> )—C	0.32	107.7	b	b
C—C(=O <sup>+</sup> )—H	0.08	116.9	b	b
C—C—C(=O <sup>+</sup> )	0.36	109.0	111.0	101.6
H—C—C(=O <sup>+</sup> )	0.59	109.0	106.2	106.7
O—C—C(=O <sup>+</sup> )	1.20	104.1	104.1	104.1
C—C—O <sup>+</sup>	1.08	104.1	104.1	104.1
C—O <sup>+</sup> =C	0.73	113.9	b	b
C—C=O <sup>+</sup>	1.09	113.5	120.1	b
H—C(=O <sup>+</sup> )—H	0.40	124.5	b	b
H—C=O <sup>+</sup>	0.22	111.7	120.1	b
H—C=O <sup>+</sup>	1.01	101.0	100.7	102.8
Torsional parameters				
Atom Types	$V_1$	$V_2$	$V_3$	
C—C—C(=O <sup>+</sup> )—C	1.2000	0.2000	0.1500	
O—C—C—C(=O <sup>+</sup> )	1.0000	−1.5000	1.0000	
H—C=O <sup>+</sup> —C	0.0000	13.3938	0.0000	
C—C=O <sup>+</sup> —C	2.1252	8.3938	−0.0084	
C—C—O <sup>+</sup> =C	−0.4278	0.6058	−0.6941	
O—C—C=O <sup>+</sup>	1.0000	5.1000	0.0000	
C—C(=O <sup>+</sup> )—C—O	0.0000	0.0000	0.0000	
C—C—C(=O <sup>+</sup> )—H	0.7300	0.2700	0.6800	
C—C(=O <sup>+</sup> )—C—H	0.0000	0.0000	0.1300	
C—C—C—C(=O <sup>+</sup> )	0.0500	0.3700	0.0000	
H—C—C—C(=O <sup>+</sup> )	0.0000	0.0000	0.3068	
H—C—C(=O <sup>+</sup> )—H	0.1800	0.0000	0.2750	
O—C—C(=O <sup>+</sup> )—H	0.0000	0.0000	0.0000	
H—O—C—C(=O <sup>+</sup> )	0.0000	0.0000	0.0900	
C—C—C—O <sup>+</sup>	−0.2341	−0.3859	0.9941	
O—C—C—O <sup>+</sup>	4.0000	−3.0000	1.2000	
C—C—C=O <sup>+</sup>	0.1161	0.4952	−0.0848	
H—C—C—O <sup>+</sup>	0.0000	0.0000	0.5359	
H—C—C=O <sup>+</sup>	0.0000	0.0000	−0.0648	
H—C—O <sup>+</sup> =C	0.0000	0.0000	−0.4659	

the MM3 calculated torsional profiles are in close agreement with those derived using Gaussian 92 (Figs. 2–5). *Ab initio* calculated bond lengths (Table II), bond angles (Table III), moments of iner-

**TABLE I.**  
**(Continued)**

## Out-of-plane bending parameters

Atom Types	$q_0$ (degrees)
71—1	2.25
71—5	1.28
71—70	1.55

## Electronegativity correction parameters

Atom Types Defining Bond	End of Bond	Attached Atom	Correction to $I_0$
C—O <sup>+</sup>	C	C	0.0150
C—C	C	O <sup>+</sup>	-0.0300
C—C	C	C(=O <sup>+</sup> )	0.0400
C=O <sup>+</sup>	C(=O <sup>+</sup> )	C	0.0060
C—C(=O <sup>+</sup> )	C	O	0.0190
C—C(=O <sup>+</sup> )	C(=O <sup>+</sup> )	=O <sup>+</sup>	-0.0400
H—C	C	=O <sup>+</sup>	-0.0100
H—C	C	C(=O <sup>+</sup> )	-0.0060
O—C	C	C(=O <sup>+</sup> )	-0.0160

## van der Waals

Atom Type	$e$	$r$
O <sup>+</sup>	0.066	1.7400

## Heat of formation

Atoms Defining Bond	Bond Enthalpy	Strainless Bond Enthalpy
H—C(=O <sup>+</sup> )	-3.205	-3.125
C—C(=O <sup>+</sup> )	-3.889	-3.920
C—O <sup>+</sup>	56.840	56.840
C=O <sup>+</sup>	113.690	113.690

## Dipole parameters

Atoms Defining Bond	Bond Moment
C—C(=O <sup>+</sup> )	-1.4000
H—C(=O <sup>+</sup> )	0.9600
C—O <sup>+</sup>	1.6200
C=O <sup>+</sup>	-2.9200

<sup>a</sup> The atom types include O<sup>+</sup>(70), C(=O<sup>+</sup>)(71). C(=O<sup>+</sup>) refers to as carbon atom in C=O<sup>+</sup> moiety. During this parameterization, Atom types 70 and 71 were modified from 70 and 71 in MM2, respectively. All physical constants and parameters not included in this table are the same as their corresponding MM2 values.

<sup>b</sup> Does not apply.

tia (Table IV), dipole moments (Table V), and vibrational frequencies are also reproduced well by MM3.<sup>14</sup>

**BOND LENGTHS**

Selected oxocarbenium ion bond lengths are reported in Table II. The oxocarbenium-specific atom types (oxocarbenium carbon, type 71, and oxygen, type 70) required several new equilibrium bond length parameters. Under the influence of the local chemical environment, these bond lengths will vary from molecule to molecule. The bond length and electronegativity parameters have been adjusted so that MM3 is able to well reproduce all oxocarbenium ion bond lengths. For example, in the 12 molecule training set, the bond length 70—71 (C=O<sup>+</sup>) calculated with *ab initio* methods varies from 1.249 to 1.276 Å, a range of 0.027 Å between the shortest bond (7 and 8) and the longest bond (4). Utilizing electronegativity parameters, MM3 reproduces all 70—71 bond lengths in the training molecules with an RMS deviation of 0.013 Å. In *ab initio* calculations, the bond length 71—1 ([O<sup>+</sup>=]C—C<sub>sp3</sub>) varies from 1.461 to 1.483 Å. By careful parameterization of electronegativity parameters, MM3 reproduces these bond lengths with an RMS deviation of 0.020 Å. Two additional bond types, 70—1 ([C=]O<sup>+</sup>—C<sub>sp3</sub>) and 71—5 ([O<sup>+</sup>=]C—H), were also modeled in the same way. As shown in Table II, the MM3 calculations using these parameters are in close agreement with the *ab initio* results, with RMS deviations of 0.007 and 0.004 Å for 70—1 and 71—5, respectively.

In addition to the new oxocarbenium ion-related bond types introduced here, other bond lengths should be monitored during parameterization. The C<sub>sp3</sub>—C<sub>sp3</sub> bond length (1—1), for example, is one of the fundamental bonds in molecular mechanics with an equilibrium bond length of 1.5247 Å ( $r_g$ ) and a stretching force constant of 4.49 mdy/Å. For an ethyl group attached to the oxocarbenium oxygen, the 1—1 bond length is shortened by about 0.012 Å due to an electronegativity effect. In contrast, the same bond length increases by approximately 0.032 Å when an ethyl group is bound to the oxocarbenium carbon. Using appropriate electronegativity parameters, MM3 reproduces these bond lengths with an average deviation of 0.007 Å from the *ab initio* results.

**Bond Angles**

Accurate modeling of bond angles is also an important consideration in molecular mechanics pa-

**TABLE II.** Comparison of Selection Bond Lengths:<sup>a</sup> Molecular Mechanics and *Ab Initio* Geometries of the Twelve Training Molecules.

Molecule	C=O <sup>+</sup>		C—R <sub>1</sub>		C—R <sub>2</sub>		<sup>+</sup> O—R <sub>3</sub>	
	MM3 ( <i>r<sub>g</sub></i> )	MP2 ( <i>r<sub>e</sub></i> )	MM3 ( <i>r<sub>g</sub></i> )	MP2 ( <i>r<sub>e</sub></i> )	MM3 ( <i>r<sub>g</sub></i> )	MP2 ( <i>r<sub>e</sub></i> )	MM3 ( <i>r<sub>g</sub></i> )	MP2 ( <i>r<sub>e</sub></i> )
1	1.260	1.250	1.093	1.092	1.094	1.088	1.494	1.498
2	1.260	1.262	1.092	1.096	1.464	1.462	1.493	1.490
3	1.261	1.264	1.466	1.465	1.092	1.092	1.491	1.492
4	1.260	1.276	1.462	1.481	1.460	1.475	1.490	1.482
5	1.263	1.264	1.092	1.096	1.465	1.461	1.493	1.488
6	1.263	1.266	1.467	1.464	1.092	1.092	1.491	1.490
7	1.260	1.249	1.093	1.093	1.094	1.088	1.510	1.526
8	1.260	1.249	1.093	1.092	1.094	1.088	1.516	1.526
9	1.259	1.250	1.093	1.092	1.094	1.088	1.510	1.509
10	1.260	1.257	1.091	1.096	1.481	1.483	1.493	1.494
11	1.260	1.262	1.092	1.096	1.464	1.462	1.509	1.499
12	1.263	1.264	1.092	1.097	1.472	1.456	1.493	1.488

<sup>a</sup> All values in Ångstrom.

parameterization. The *ab initio* bond angles of all 12 training molecules were used as templates without any scaling. Skeletal bond angles formed by heavy atoms were treated as more important than other bond angles. Among those skeletal bond angles, angle 71—70—1 (C<sub>sp2</sub>—O<sup>+</sup>—C<sub>sp3</sub>) is most important. Using the final optimized parameters, MM3 is in close agreement with *ab initio* results for this angle with an average deviation of 0.4 degree and

the largest deviation of 0.7 degree (Table III). It is noteworthy that the value of the 71—70—1 angle will depend upon the conformation of the model molecule (*cis* vs. *trans*). Because MM3 does not have torsion–bend interaction terms, this dependence is not duplicated as well as it could be. Therefore, the selection of a bond angle parameter has involved compromise so that deviations in the two conformations are averaged. Using our new parameter, the

**TABLE III.** Comparison of Selection Bond Angles:<sup>a</sup> Molecular Mechanics and *Ab Initio* Geometries of the Twelve Training Molecules.

Molecule	R <sub>1</sub> —C—O <sup>+</sup>		R <sub>2</sub> —C—O <sup>+</sup>		R <sub>3</sub> —O <sup>+</sup> —C	
	MM3	MP2	MM3	MP2	MM3	MP2
1	122.3	121.3	115.5	116.0	121.0	121.7
2	119.2	118.3	120.8	120.3	121.5	121.4
3	125.4	127.6	111.8	112.1	122.6	123.1
4	121.1	122.3	116.8	115.6	123.3	122.6
5	118.9	118.1	120.8	120.6	121.6	121.3
6	125.3	127.8	111.6	111.9	122.7	122.7
7	122.3	121.2	115.5	116.4	121.3	121.5
8	122.3	121.2	115.5	116.4	121.2	121.5
9	122.3	121.2	115.6	116.3	121.1	121.3
10	119.0	120.5	121.1	119.9	121.4	121.2
11	119.3	118.2	120.7	120.4	121.6	121.1
12	118.9	118.0	120.6	119.7	121.6	121.3

<sup>a</sup> All values in degree.

MM3 calculated bond angle is too small for the *cis* conformation and too large for the *trans* conformation.

Another important skeletal bond angle is 70—1—1 ( $\text{O}^+ - \text{C}_{\text{sp}^3} - \text{C}_{\text{sp}^3}$ ). Although the hydroxyl and methyl groups attached to the terminal  $\text{sp}^3$  carbon introduce a tremendous perturbation to the skeletal structure, the MM3 calculated bond angles are still in close agreement with *ab initio* results, with an average deviation and largest deviation of 0.4 and 0.5 degree, respectively. In summary, the MM3 and *ab initio* results are in close agreement for all new bond angles incorporating the two atom types 70 and 71.

Two established bond angles encountered in this parameterization had large deviations, but they are both beyond the scope of this work. The first was bond angle 1—1—1 ( $\text{C}_{\text{sp}^3} - \text{C}_{\text{sp}^3} - \text{C}_{\text{sp}^3}$ ) as seen in **8**. The MM3 calculated angle is 112.0 degrees, while the *ab initio* derived result is 109.0 degrees. The second bond angle was 1—1—6 ( $\text{C}_{\text{sp}^3} - \text{C}_{\text{sp}^3} - \text{OH}$ ) in **9**, **11**, and **12**, with an average deviation of 5.5 degrees. Compared to the *ab initio* calculated results, the MM3 1—1—6 angle in these three molecules is too large by 6.2, 5.4, and 4.9 degrees, respectively.

## MOMENTS OF INERTIA

MM3 and *ab initio* calculated moments of inertia are shown in Table IV. Most of the twelve training molecules exhibit only small differences between the MM3 results and *ab initio*-derived moments of inertia, with the most significant deviations seen in **3** and **5**. Because moments of inertia are only

dependent on the mass of atoms and their relative positions, the deviations in moments of inertia in these two molecules are due to differences in geometry. Bond length deviations of **3**, for example, are very small with the largest non-hydrogen deviation of 0.003 Å. One bond angle ( $\text{O}^+ - \text{C}_{\text{sp}^2} - \text{C}_{\text{sp}^3}$ ), however, deviates by approximately 2.2 degrees (as mentioned previously, this deviation could be reduced by including the torsion-bend interaction in MM3). This bond angle deviation causes the moments of inertia to shift by 2.92, -3.40, and -2.14% for  $I_x$ ,  $I_y$ , and  $I_z$ , respectively. In another example, MM3 reproduces *ab initio* geometric data well for **5** with the largest bond length deviation of 0.005 Å and the largest skeletal bond angle deviation of 0.9 degree. Even though no single bond length or angle is significantly different,  $I_x$  in **5** still deviates by -5.26%. Upon close examination of the bond angle deviations, we observe that all but one MM3 calculated skeletal bond angle is larger than those derived by the *ab initio* method. Each of these deviations is very small individually, but because they accumulate rather than cancel out, the moments of inertia of **5** are noticeably affected. This enhancement of error is the reason that  $I_x$  is too small and  $I_y$  and  $I_z$  are too large in the MM3 results. Similarly, most of the MM3 calculated skeletal bond lengths are too long, causing  $I_y$  and  $I_z$  to be too large, although there is generally little effect on  $I_x$ . The other notable, yet much smaller deviations in moments of inertia are seen in **9**, **11**, and **12**. Each of these molecules contains a  $\text{C}_{\text{sp}^3} - \text{C}_{\text{sp}^3} - \text{OH}$  (1—1—6) angle, which as discussed previously, shows an average

**TABLE IV.** Moments of Inertia<sup>a</sup> of the Twelve Training Molecules.

Molecule	$I_x$		$I_y$		$I_z$	
	MM3	MP2	MM3	MP2	MM3	MP2
1	9.702	9.514	49.460	49.442	55.799	55.684
2	13.414	13.341	124.553	123.981	131.338	130.963
3	31.362	30.473	85.376	88.385	110.047	112.454
4	60.081	61.725	127.686	128.054	177.762	180.219
5	28.927	30.532	225.288	219.051	233.827	227.188
6	49.095	48.545	171.276	173.504	189.554	190.360
7	21.389	21.514	112.533	111.885	116.970	116.059
8	26.668	27.001	229.899	226.855	234.104	230.181
9	23.596	24.287	227.058	223.724	232.478	228.114
10	20.943	21.235	229.812	228.503	244.067	243.129
11	30.421	31.562	391.540	387.320	400.402	395.089
12	31.881	30.789	399.162	404.288	405.951	410.460

<sup>a</sup> All values in  $\text{au} \cdot \text{\AA}^2$ .



**TABLE V.**  
**Dipole Moments<sup>a</sup> of the Twelve Training Molecules.**

Molecule	MM3	MP2	Deviation
1	3.29	2.68	0.61
2	3.88	2.18	1.70
3	1.73	1.66	0.07
4	1.56	1.60	-0.04
5	3.88	2.67	1.21
6	1.73	0.91	0.82
7	3.29	4.16	-0.87
8	3.29	6.17	-2.88
9	2.77	6.23	-3.46
10	2.40	1.93	0.47
11	2.90	5.07	-2.17
12	5.15	5.61	-0.46

<sup>a</sup> All values in Debye.

5.5 degree deviation between MM3 and *ab initio* values. In each case, however, the error primarily appears in  $I_x$ .

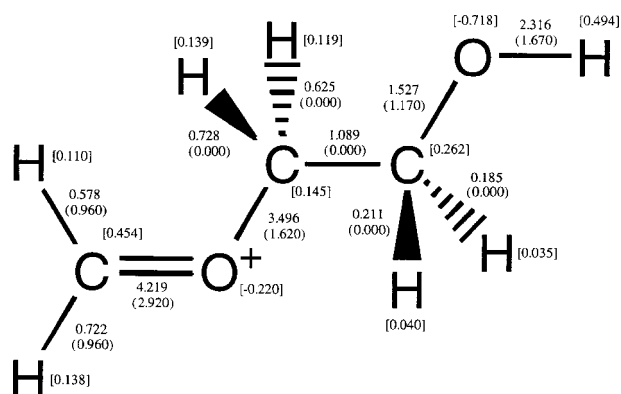
## DIPOLE MOMENTS

The MM3 and *ab initio* calculated dipole moments for the 12 molecules in the training set are listed in Table V. As shown in this table, some of the differences in the dipole moment are unusually large. One could speculate that the primary reason for the observed differences is due to a limitation of MM3, as charge-induced electron density shifts are not generally accounted for in molecular mechanics. MM3 currently only has induced dipole parameters for a limited range of bonding motifs. This is

a particular problem for charged species; although a positive charge formally resides on the oxocarbenium oxygen, this charge is effectively distributed over the entire molecule. This net charge and its splitting cause the charge distribution of oxocarbenium ion to be significantly different from the corresponding neutral molecule. In addition, *ab initio*-calculated dipole moments are also known to be inaccurate, and are particularly difficult to determine for ions.

To further compare the differences of charge distributions and dipole moments between *ab initio* calculations and MM3 results, a detailed electronic population analysis was carried out for training molecule 9. As shown in Figure 6, partial charges (in square brackets) for all atoms were taken from *ab initio* ChelpG results. Then, charge separations and bond moments were calculated from these partial charge data. Significant differences were observed between the *ab initio*-derived bond moments (without parentheses) and MM3 bond moments (in parentheses). For example, the average bond moment of O—H in a neutral molecule (also the default MM3 bond moment parameter for this bond) is 1.670 Debye, while the same bond moment in the corresponding oxocarbenium ion (9) is 2.316 Debye according to the *ab initio* calculation. A permanent bond moment of 0.0 Debye is assigned to the  $C_{sp^3}$ — $C_{sp^3}$  bond in MM3, while the *ab initio*-derived value is 1.089 Debye for this ion. The MM3 bond moments for  $C_{sp^3}$ — $C_{sp^3}$ ,<sup>4</sup>  $C_{sp^3}$ —O, and O—H<sup>15</sup> were developed in previous studies using other training sets, and will not vary among molecules. This is not problematic, as the moment parameters are transferable in most neutral molecules. In summary, induced dipoles cause significant differences between the MM3 dipole moments and *ab initio* results, but these deviations have not been fully accounted for in the current version of MM3.

Although MM3 cannot reproduce *ab initio* calculated dipole moments, this may not be as bad as one would think, given the known deficiencies with *ab initio* dipole moment calculations. The deviations between MM3 and *ab initio* dipoles do not adversely affect the other components of the calculation. Normally, the bond moment parameters affect the shapes of torsional energy profiles and the vibrational frequencies, while they have little influence on bond lengths and bond angles. Through the use of TORSMAST and MPMSR for the parameterization, the force field was generated in such way as to maximally absorb the errors. In the oxocarbenium ion parameterization, even if some of the dipole moments deviate significantly, as mentioned

**FIGURE 6.** Bond moment and partial charge comparisons between the MM3 and Gaussian calculations of 9.

previously, the MM3 torsional energy profiles and vibrational frequencies are still in close agreement with the *ab initio* values.

### VIBRATIONAL FREQUENCIES

Vibrational frequencies are essential to accurate parameterization, especially in the development of stretching force constants, bending force constants, and electronegativity constants. If these values are optimized, *ab initio* calculated vibrational frequencies can be reproduced in molecular mechanics for every vibrational mode. But these parameters, especially electronegativity constants, will affect geometric data (e.g., bond lengths) in addition to vibrational frequencies. Therefore, molecular mechanics parameterization must consider all of the variables and their potential effects to determine the overall best parameter set.

In this work, all *ab initio* vibrational frequencies were calculated in Gaussian 92. VIBPLT<sup>16</sup> was used to display MM3 vibrational modes on screen, and GAUSSVIB<sup>17</sup> was used to convert Gaussian 92 output to a format suitable for VIBPLT. It is very important to assure that each MM3 vibrational mode corresponds with an *ab initio* mode. By animating the vibrational modes, each MM3 calculated mode can be paired with an *ab initio* mode that has similar characteristics, and differences in frequencies between the two methods can be determined. To optimize MM3 vibrational frequencies, parameters were adjusted until the pairwise deviation is minimized over all modes.

Vibrational mode assignments, symmetries, *ab initio* calculated frequencies, MM3 frequencies, and the deviations between these two methods for all vibrational modes of each molecule in the training set have been determined.<sup>14</sup> Close agreement between the MM3 vibrational frequencies and the *ab initio* data was achieved, with RMS deviations between the two methods of 33, 32, 44, 42, 25, 28, 40, 37, 43, 38, 37, and 27 cm<sup>-1</sup> for compounds **1** through **12**, respectively.

Although MM3 reproduces *ab initio* calculated vibrational frequencies well for most vibrational modes, some modes deviate more than others. For example, the last mode in compound **3** indicates that this conformation is a local minimum in *ab initio* calculation ( $\nu = 64$  cm<sup>-1</sup>), but it is a transition state in the MM3 force field ( $\nu = -67$  cm<sup>-1</sup>). There are two methyl groups that are *cis* to each other in compound **3**, each with a rotation barrier of less than 1 kcal/mol. Individually, MM3 reproduces the *ab initio* calculated torsional energy

profile very well for each methyl group. When both groups are present *cis* to each other, however, the interaction between the hydrogen atoms in these two methyl groups causes the deviation in results. Both methods, MM3 and *ab initio*, agree that the system is lower in energy when a C—H bond in either methyl group eclipses the C=O<sup>+</sup> bond, due to the favorable dipole-induced dipole interaction between these two bonds. However, if the C—H bonds in both methyl groups stay in an eclipsed position, the two hydrogen atoms that point toward each other cause strong steric repulsion and increase the potential energy. An *ab initio* calculation finds that the steric repulsion is stronger than the favorable interaction between the C—H and C=O<sup>+</sup> bonds, causing one of the methyl groups to rotate about 60 degrees and the C—H bond to point away from the other methyl group. However, the MM3 force field treats the interaction between C—H and C=O<sup>+</sup> as stronger than the steric interaction between two hydrogen atoms, so one conformation is a minimum in *ab initio* and a transition state in MM3. Although MM3 and *ab initio* are not in agreement with each other on this vibrational mode, the deviation is not significant because it is not a skeletal mode. Additionally, the energy difference involved is minor, and can be easily perturbed by other interactions. In fact, if **3** is a fragment within a larger system, the deviation will not affect the conformation of the whole molecule. Overall, the *ab initio* and MM3 vibrational frequencies are in good agreement, with an average RMS deviation of 33 cm<sup>-1</sup> over the 12 molecules in the training set.

### Conclusions

A set of MM3 force field parameters for oxocarbenium ions has been developed based on *ab initio* calculations of the twelve training molecules at the MP2/6-31+G\* level of theory. The molecular mechanics parameterization tool TORSMAST was used to develop torsional parameters by fitting molecular mechanics calculated torsional profiles to those derived from *ab initio* calculations. Torsional energy profiles were carefully reproduced so that accurate conformational searches could be carried out. The program MPMSR was used to generate other necessary parameters. Using the optimized set of parameters, MM3 can accurately reproduce the structural and vibrational data for oxocarbenium ions, the intermediate state of acid-catalyzed carbohydrate hydrolysis. In addition, accurate force constants and heat of formation parameters have

been developed so that carbohydrate hydrolysis reaction simulation can be carried out and reaction rates can be predicted.

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